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Glucagon-like peptide-1 secretagogues from the leaves of *Oparanthus teikiteetinii*

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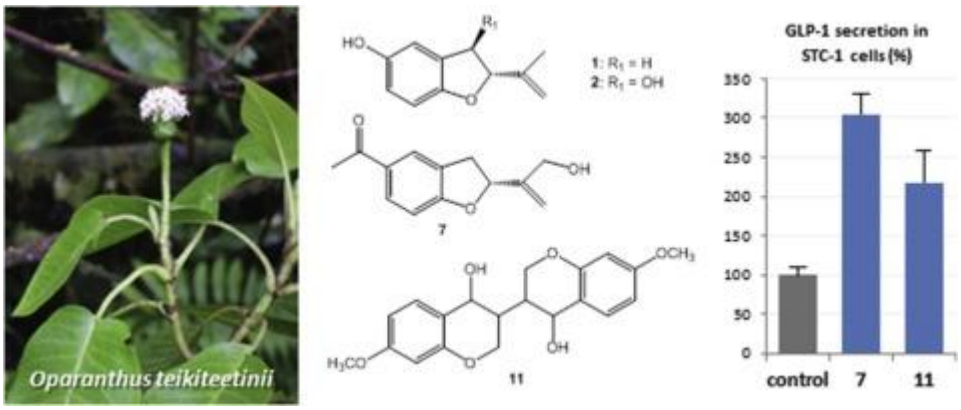
Abstract :

In our search for natural compounds that stimulate glucagon-like peptide-1 secretion, an extract from the leaves of Oparanthus teikiteetinii (Asteraceae) was found to increase significantly GLP-1 secretion in vitro in a model cell line (mouse intestinal STC-1 cells). The phytochemical investigation of this extract resulted in the isolation of two new dihydrobenzofuran derivatives (1-2) identified as (2R)-2-(prop-1-en-2-yl)-2,3-dihydro-1-benzofuran-5-ol (1) and (2S,3R)-2-(prop-1-en-2-yl)-2,3-dihydro-1-benzofuran-3,5-diol (2). Thirteen other compounds were isolated, including eight known dihydrobenzofuran derivatives (3-10), jasopyran (11), and four sesquiterpene lactones (12-15) including a new one, grandulin (15). Their structures were established mainly by NMR and HRESIMS analysis and by comparison with data reported in the literature. Tested on STC-1 cells at the concentration of 100 mu M, compounds 7, 11, and 12 increased GLP-1 secretion by 305, 218, and 156% respectively, compared to control cells, without affecting cell viability.

Graphical abstract



Highlights

► This is the first report on phytochemistry and bioactivity of *Oparanthus teikiteetinii*. ►Two dihydrobenzofuran derivatives (**1–2**) were identified for the first time. ► Several compounds stimulate GLP-1 secretion in STC-1 cells without cytotoxicity. ► 12-hydroxy-tremetone (**7**) is the most active with a stimulation of 305 ± 26%.

Keywords : Oparanthus teikiteetinii, Benzofuran derivatives, Coumaran, Sesquiterpene lactones, Glucagon-like peptide-1 secretion

1. Introduction

Oparanthus teikiteetinii (J.Florence & Stuessy) R.K.Shannon & W.L.Wagner is a tree endemic to the Marquesas Islands, French Polynesia, which belongs to the Asteraceae family and to the subtribe Coreopsidinae. Firstly described under the genus *Bidens* (Florence and Stuessy, 1988), it has been recently revised to the genus *Oparanthus* (Ryding and Bremer, 1992; Shannon and Wagner, 1997). No traditional uses have been reported for this species that has been found only in the restricted area of the Toovi plateau on the island of Nuku Hiva, and no phytochemical nor pharmacological studies have been conducted until now. According to phylogenetic trees, *O. teikiteetinii* is rather closely-related to *Fitchia speciosa*, endemic to the Cook Islands (Kimball and Crawford, 2004). This latter species was found to contain mainly sesquiterpene lactones, as most of the Asteraceae, and dihydrobenzofuran derivatives (Bohlmann et al., 1980). As part of our continuous efforts to identify natural GLP-1 secretagogues, we decided to evaluate the potential of *O. teikiteetinii* to stimulate the secretion of glucagon-like peptide-1 (GLP-1) *in vitro* in a mouse intestinal cell culture model. GLP-1 is an intestinally secreted peptide involved in blood glycemia regulation (Nicolaus et al., 2011). As its secretion is impaired in patients with type 2 diabetes, compounds improving GLP-1 secretion levels could therefore represent a novel therapeutic strategy (Nauck et al., 1993; Nauck et al., 1997; Vilsbøll et al., 2001). In our *in vitro* assay, the EtOAc extract from the leaves of *O. teikiteetinii* increased significantly the extracellular secretion of GLP-1 in STC-1 cells. The phytochemical investigation of this extract led to the isolation of 15 compounds, including mainly benzofuran and benzopyran derivatives (**1-11**), together with 4 sesquiterpenoids (**12-15**). All compounds were evaluated for GLP-1 secretagogue activity and some of them (**7**, **11**, and **12**) were found to be significantly active. This is the first report on phytochemical composition and biological activity of *Oparanthus teikiteetinii*.

2. Results and discussion

The EtOAc extract from the leaves of *O. teikiteetinii* increased the extracellular secretion of GLP-1 in STC-1 cells by 249 ± 2% when tested at a concentration of 30 µg/mL (Supplem. S1). This extract was subjected to successive chromatographic separations leading to fifteen compounds (**1-15**) (Figure 1 and Supplem. S2), including two new dihydrobenzofuranes identified as (2R)-2-(prop-1-en-2-yl)-2,3-dihydro-1-benzofuran-5-ol (**1**) and (2S,3R)-2-(prop-1-en-2-yl)-2,3-dihydro-1-benzofuran-3,5-diol (**2**). Eight other coumaran derivatives were isolated and identified by careful comparison of their spectral data with those reported in the literature as tremetone (**3**) (Banskota et al., 1998; Bonner et al., 1961; Lee et al., 2010), 3-hydroxytremetone (**4**), 6-hydroxytremetone (**5**), 3,6-diydroxytremetone (**6**), 12-hydroxytremetone (**7**), 3-hydroxytremetol (**8**), megapodiol (**9**), and 6-hydroxy-megapodiol (**10**) (Jarvis et al., 1986; Spring et al., 1991). According to optical rotation and comparison with data in literature, all the isolated 2-substituted dihydrobenzofuran derivatives were found to have a 2R

absolute configuration and the 3-OH, 2-substituted derivatives a 2S,3R configuration, which is in accordance with previous literature reports (Wang et al., 2016). A bibenzopyran derivative, jasopyran (**11**), was also obtained (Ahmed et al., 2004), together with four sesquiterpene lactones: costunolide (**12**) (Rao et al., 1958, 1960), dihydrocostunolide (**13**), asperilin (**14**) (Herz and Kagan, 1967; Herz and Viswanathan, 1964), and grandulin (**15**). The structure of the latter was wrongly reported as a constituent of *Inula grandis* (Nikonova and Nikonov, 1970; Nikonova and Nikonov, 1972). Therefore, the natural occurrence of grandulin is herein reported for the first time.

Compound **1** was isolated as colorless oil. Its UV spectrum presented maxima of absorption at 228 and 300 nm. Its molecular formula was determined to be $C_{11}H_{12}O_2$ on the basis of the observed peak at *m/z* 177.0909 $[M+H]^+$, indicating six degrees of unsaturation. The ^{13}C and ^{1}H NMR data displayed typical signals of a 2,3-dihydrobenzofuran ring, confirmed by HMBC correlations. The proton and carbon signals are shown in Table 1. The aromatic ring was shown to be hydroxylated in *para* (δC 150.9), and the furan ring substituted in C-2 (δC 85.4) by a methylethenyl group composed of one olefinic quaternary carbon (δC 144.7), one olefinic methine (δC 110.4), and one methyl (δC 15.9). The methylene signal observed in DEPT and ^{1}H spectrum was assigned to position 3 (δC 34.8; δH 3.25, dd, *J* = 15.7, 8.3 Hz; 2.96, dd, *J* = 15.7, 8.3 Hz). Thus compound **1** was identified as 2,3-dihydro-2-(1-methylethenyl)-5-benzofuranol. This compound has been previously reported as a synthetic intermediate in the synthesis of coumaranol derivatives (Schädel and Habicher, 2002), but is now reported for the first time as a natural product and named oparanol.

Compound **2** was obtained as slightly orange oil and presented a UV spectrum similar to the one of compound **1**. Its molecular formula was deduced to be $C_{11}H_{12}O_3$ (*m/z* 191.0707, $[M-H]^-$). The ^{1}H and ^{13}C NMR spectra of compound **2** were remarkably similar to those of compound **1**, confirming a 5 hydroxyl-benzofuran skeleton substituted by a methylethenyl group in C-2 (see Table 1 for ^{13}C and ^{1}H data). The downfield values for C-3 (δC 76.6) indicated the presence of an hydroxyl group in position 3, confirmed by the absence of a methylene signal in the ^{1}H spectrum but the presence of an oxygenated methine signal at 5.02 (d, *J* = 4.3 Hz). The relative configuration was assumed to be *trans* on the basis of the small coupling constant observed between H-2 and H-3 (4.3 Hz), according to the Karplus equation and to literature (Zalkow et al., 1972). Therefore, **2** was elucidated as 2,3-dihydro-2-(1-methylethenyl)-benzofuran-3,5-diol and named 3-hydroxy-oparanol.

All compounds were evaluated for their capacity to stimulate GLP-1 secretion in an *in vitro* model of STC-1 cells in culture (Table 2). The dihydrobenzofuran derivative 12-hydroxy-tremetone (**7**) was found to be the most active resulting in a 3-fold increase in GLP-1 secretion in STC-1 cells (305 ± 26%). Jasopyran (**11**) and costunolide (**12**) were also found to contribute to the bioactivity of the extract, as they stimulated GLP-1 secretion by 218 ± 41% and 156 ± 39% respectively. Furthermore, none of the isolated compounds affected STC-1 cells viability at the tested concentration, reinforcing

their therapeutic potential. However, in order to confirm the potential of *O. teikiteetinii* compounds as antidiabetic agents, further *in vitro* and *in vivo* assays are required to identify mechanisms of actions and to assess lack of toxicity. As *O. teikiteetinii* is considered as a threatened species due to its extremely narrow distribution, alternative sourcing is mandatory. Chemical synthesis could be considered thank to the rather simple structure of active constituents (Sangeeta and Deepti, 2017). Also, alternative natural sources could be used. Compound **7**, the most active constituent in our bioassay, has been previously reported from various *Helichrysum* species, already used for essential oil production (Valverde Lopez and Rodriguez Gonzalez, 1971; Zapesochnaya et al., 1990). Supercritical CO_2 extraction from *Helichrysum italicum* flowers can be performed to yield an extract containing up to 23% of compound **7** (Jerković et al., 2016), providing therefore another source to study in depth its therapeutic potential. This would enable the preservation of biodiversity while contributing to the development of potential new drugs for the management of type 2 diabetes.

3. Experimental

3.1. General experimental procedures

Optical rotations were measured on a Jasco P-2000 polarimeter (λ 589 nm, path length 1.0 cm). NMR experiments were conducted on a Bruker 500 MHz Avance II spectrometer equipped with a $^{13}C/^{1}H$ cryoprobe. HRESIMS analyses were carried out on an Agilent 6520 Q-ToF mass spectrometer. Preparative HPLC was conducted on a Gilson 322 LC system using an Axia Phenomenex C18 column (100 mm × 21.2 mm). Mobile phase consisted of a mixture of acetonitrile (ACN) and water (H_2O) containing 0.05% v/v formic acid at a flow rate of 25 mL/min. Vacuum liquid chromatography (VLC) was performed using 40–60 µm silica gel (Sigma Aldrich). Sephadex LH-20 (Sigma Aldrich) was used for gel filtration chromatography. Thin-layer chromatography (TLC) was performed on pre-coated silica gel plates (silica gel 60 F254, Merck). HPLC grade solvents were purchased from Sigma Aldrich.

3.2. Plant material

Fresh leaves (1.75 kg) of *Oparanthus teikiteetinii* were collected in January 2015 in Nuku-Hiva, Marquesas Islands, French Polynesia, and identified by Dr Jean-François Butaud, botanist. The harvesting permit n°0923 was delivered from DIREN in November 2014. A voucher specimen (No CM1717_OT 01-2015) is deposited at the herbarium of the University of French Polynesia.

3.3. Extraction and isolation

The air dried leaves of *Oparanthus teikiteetinii* (153.9 g) were crushed and extracted by maceration with EtOAc (100 mL/50 g, 3 x 3 hours). The filtrates were combined and evaporated to obtain a crude EtOAc extract (28.15 g). The EtOAc extract was fractionated using vacuum liquid chromatography

(150 g of silica 60 Å, 40-63 µm, 230-400 mesh), each fraction obtained by eluting with 300 mL of the following solvents: cyclohexane (c-Hex), c-Hex-$CHCl_3$ (1:1), $CHCl_3$, $CHCl_3$-EtOAc (75:25), $CHCl_3$-EtOAc (1:1), EtOAc and CH_3OH (500 mL) to afford seven fractions; F1 (0.71 g), F2 (0.66 g), F3 (6.86 g), F4 (14.18 g), F5 (2.47 g), F6 (1.09 g), and F7 (2.08 g). F3 (750 mg) was fractionated on Sephadex-LH 20 eluting with $CHCl_3$/CH_3OH (1:1) to obtain twelve sub fractions (F3S1-F3S12). Sub fraction S-10 (62.1 mg) was purified by preparative HPLC (20% ACN during 3 min, to 65% ACN in 12 min) to yield compound **12** (41.2 mg). Sub fraction S-11 (201.2 mg) was purified in the same conditions to afford compounds **3** (108.3 mg), **5** (24.9 mg), and **12** (40.9 mg). F4 (800 mg) was fractionated using Sephadex LH-20 $CHCl_3$/CH_3OH (1:1) to afford ten main sub fractions (F4S1-F4S10). F4-S9 (402.4 mg) was purified by preparative HPLC (20% ACN during 3 min, to 65% ACN in 12 min) to yield compounds **3** (91.9 mg), **12** (109.9 mg), and **13** (6.0 mg). Using the same conditions, compounds **1** (2.5 mg), **3** (64.8 mg), **5** (8.9 mg), **8** (2.5 mg), and **12** (10.7 mg) were obtained from sub fraction F4-S10 (133.9 mg). F5 (700 mg) was also chromatographed on Sephadex-LH 20 column eluting with $CHCl_3$/CH_3OH (30:70) to obtain eight sub fractions (F5S1-F5S8). Sub fraction F5-S7 (129.6 mg) was further purified by preparative HPLC (20% ACN during 3 min, to 65% ACN in 12 min) to afford compounds **7** (1.0 mg), **8** (5.5 mg), **11** (1.6 mg), **6** (1.0 mg), and **14** (2.6 mg). Sub fraction F5-S8 (38.7 mg) was also purified on Axia column (20% ACN during 3 min, 20 to 65% in 19 min, then 65 to 80% in 4 min) to yield **15** (17.0 mg), **9** (4.1 mg), and **8** (2.5 mg). F6 (800 mg) was first fractionated on Sephadex LH-20 eluting with $CHCl_3$/CH_3OH (30:70) to obtain seven sub fractions (F6S1-F6S7). Sub fraction F6S6 (120 mg) was subjected to preparative HPLC (35 to 65% ACN in 13 min, then to 100% ACN in 5 min, flow rate 15 mL/min) to afford compounds **2** (1.0 mg), **4** (8.0 mg), and **9** (23.1 mg). Sub fraction F6S7 (20.2 mg) led to compound **10** (1.1 mg) after preparative HPLC.

3.3.1. *(2R)-2-(prop-1-en-2-yl)-2,3-dihydro-1-benzofuran-5-ol (**1**)*

Colorless oil; $[\alpha]_D^{20}$ -102.5 (c 0.18, MeOH); UV (nm): 203, 228, 300; HRESIMS *m/z* 177.0909 $[M+H]^+$, (calcd error -0.6 ppm); ^{1}H NMR and ^{13}C NMR data: see Table 1.

3.3.2. *(2S,3R)-2-(prop-1-en-2-yl)-2,3-dihydro-1-benzofuran-3,5-diol (**2**)*

Slightly orange oil; $[\alpha]_D^{20}$ -97.2 (c 0.18, MeOH); UV (nm): 203, 228, 302; HRESIMS *m/z* 191.0707 $[M-H]^-$, (calcd error -3.5 ppm); ^{1}H NMR and ^{13}C NMR data: see Table 1.

3.3.3. *(3aR,8R,8aR,9aR)-8-hydroxy-5,8a-dimethyl-3-methylene-3a,4,4a,7,8,8a,9,9a-octahydro-naphtho[2,3-b]furan-2(3H)-one (**15**)*

White amorphous powder; $[\alpha]_D^{20}$ +45.9 (c 0.10, MeOH); UV (nm): 215; HRESIMS *m/z* 249.1480 $[M+H]^+$, (calcd error -2.1 ppm); ^{1}H NMR and ^{13}C NMR data: see Table 1.

3.4. Bioassays

3.4.1. *GLP-1 secretion assay*

GLP-1 secretion assays were carried out as described previously (Tsoukalas et al., 2016). Briefly, STC-1 cells were cultured at 37°C under a 5% CO_2 atmosphere in high glucose (4.5 g/L) complete Dulbecco's modified Eagle's medium (DMEM, supplemented with 10% non-heat-inactivated fetal bovine serum (FBS), penicillin 100 IU mL^{-1}, and streptomycin 100 IU mL^{-1}). Cells were passed at subconfluency every 3-4 days. Twenty-four hours prior induction, 10^4 cells per well in 100 µL complete low glucose (1 g/L) DMEM were seeded in a 96-well plate. Prior to treatment, cells were washed two times with HBSS (Thermo Fischer 14025092), after addition of 100 µL HBSS they were returned back in the incubator for 30 min. The samples DMSO stock solutions were diluted at 100 µM in HBSS containing a constant DMSO concentration of 1 %. Finally, 125 µL of the diluted solutions were applied to the cells for 2 hours at 37°C in a 5% CO_2 atmosphere. The GLP-1 content of 100 µL of the cell supernatant was then quantified in an ELISA assay (Merck Millipore, EGLP-35K) according to the manufacturer instructions. For each molecule the assay was performed in quadruplicate and results expressed as the percentage of the GLP-1 content secreted by cells treated with HBSS containing only 1% DMSO. For the statistical analysis, a one-way ANOVA with post hoc Dunnett test was performed (* $p_{adj} \leq 0.05$; *** $p_{adj} \leq 0.001$).

3.4.2. *Cytotoxicity assay*

For the image cytometry assay, the STC-1 cells after treatment with the molecules were incubated during 20 minutes with DMEM complete medium containing propidium iodide, Hoechst reagent, and calcein (1 µM each). After incubation, pictures of each well were taken with a Celigo Imaging Cytometer (Nexcelom Bioscience) at visible and fluorescent light and processed with the Celigo program in order to quantify the percentage of viable cells.

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Table 1. ^{1}H and ^{13}C NMR data for compounds **1**, **2**, and **15** (methanol-d_4, δ in ppm, J in Hz, 500 MHz for ^{1}H NMR, 125 MHz for ^{13}C NMR).

	1		**2**		**15**	
position	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1					121.4	5.38 (m)
2	85.4	5.07 (t, 8.3)	93.4	4.75 (d, 4.3)	32.1	2.38 (m) 2.33 (m)
3	34.8	3.25 (dd, 15.7, 8.3) 2.96 (dd, 15.7, 8.3)	76.6	5.02 (d, 4.3)	77.4	3.64 (m)
4	113.6	6.63 (d, 1.5)	111.6	6.81 (m)	40.7	-
5	150.9	-	151.2	-	34.2	2.05 (m) 1.35 (m)
6	111.6	6.52 (m)	116.6	6.69 (m)	82.1	4.04 (t)
7	108.3	6.51 (m)	109.4	6.66 (m)	51.0	2.59 (br s)
8	152.9	-	153.2	-	20.7	2.12 (m) 1.68 (m)
9	127.3	-	128.7	-	50.8	2.42 (br d, 11.9)
10	144.7	-	142.7	-	133.2	-
11	110.4	5.04 (s) 4.86 (s)	110.7	5.06 (m) 4.89 (overlap)	139.6	-
12	15.9	1.74 (s)	16.2	1.79 (s)	171.4	-
13					115.6	6.03 (s) 5.52 (s)
14					22.2	1.84 (s)
15					9.96	0.89 (s)

Table 2. Glucagon-like peptide-1 secretagogue activity and cell viability induced by compounds **1-15** (tested at 100 µM on STC-1 cells).

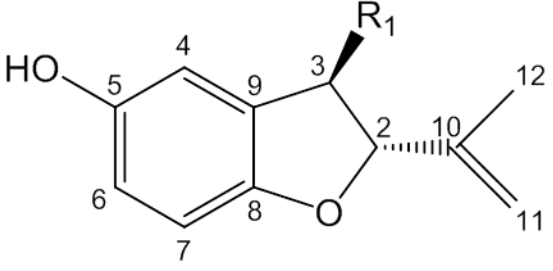
Compound	GLP-1 secretion stimulation (%)	Cell viability (%)
control	100 ± 10	96 ± 1
7[a]	305 ± 26	96 ± 1
11[a]	218 ± 41	97 ± 1
12[b]	156 ± 39	94 ± 1
15	145 ± 15	96 ± 1
1	121 ± 9	97 ± 1
10	109 ± 11	95 ± 1
14	104 ± 6	97 ± 1
4	104 ± 16	91 ± 2
13	102 ± 20	95 ± 2
3	101 ± 20	96 ± 1
9	100 ± 16	95 ± 1
6	94 ± 9	96 ± 1
2	93 ± 25	91 ± 2
8	91 ± 13	96 ± 1
5	81 ± 9	97 ± 1

Data are expressed as the mean ± SD of four independent experiments.

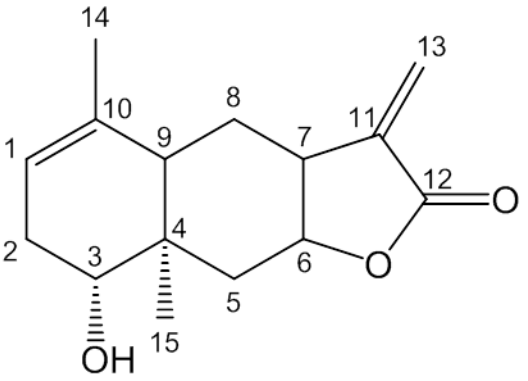
[a] *** $p_{adj} < 0.001$

[b] * $p_{adj} < 0.05$

Figure 1. Structures of compounds **1-2 and 15**.

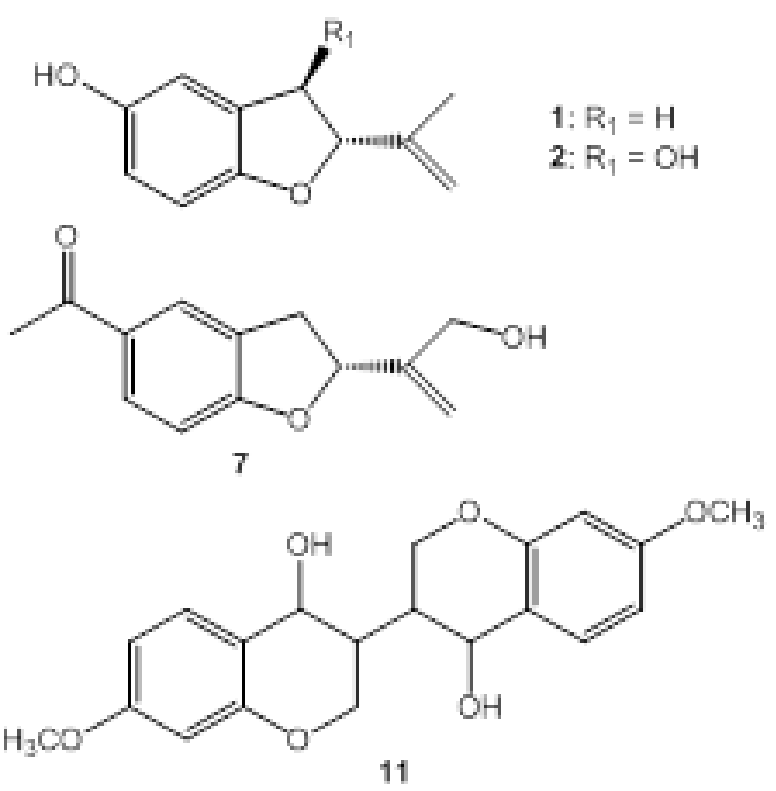


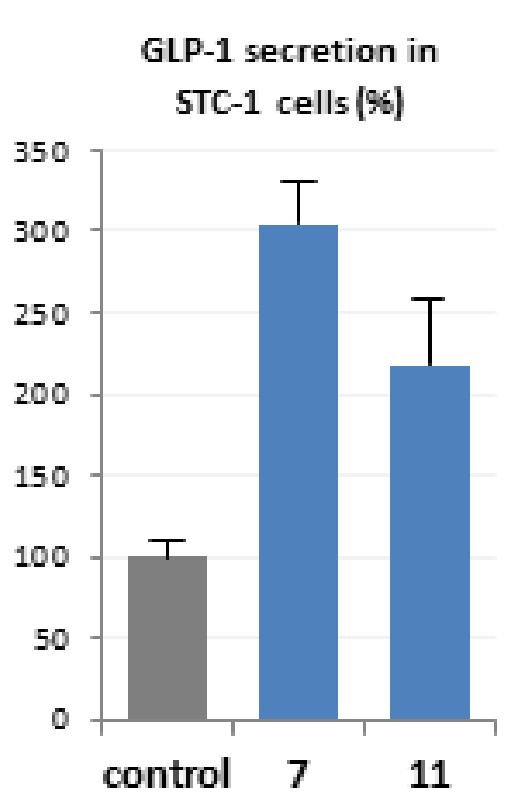
1: R_1 = H
2: R_1 = OH



15


Oparanthus teikiteetinii


HO
R1
O
1: R1 = H
2: R1 = OH
O
OH
O
7
OH
O
OCH3
OH
H3CO
O
11


GLP-1 secretion in
STC-1 cells (%)
350
300
250
200
150
100
50
0
control
7
11